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Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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Molecules

Anti-diabetic activity of alcoholic extract of *Celosia argentea* LINN.

Diabetes mellitus (DM) is a metabolic disorder affecting carbohydrate, fat, and protein metabolism. The treatment of DM is based on oral anti-hyperglycemic agents and insulin. In addition, diabetes is treated in traditional medicine with several herbal products.

The alcoholic extract of the seeds of *Celosia argentea* (Family *Amaranthaceae*), which grows throughout India and other tropical regions, has been reported to possess aphrodisiac, antipyretic, antispasmodic, anticancer, diuretic, and antibacterial properties. Also, the seeds are reported to be useful in jaundice, inflammation, gonorrhoea, and healing [1]. In folklore practice, the decoction of *C. argentea* seeds is used in diabetes mellitus, but no systematic studies have been conducted.

On this basis, Vetrichelvan and collaborators have investigated [2] the anti-diabetic activity and other beneficial effects of the alcoholic extract of *Celosia argentea* seeds (ACAS) in diabetic rats.

The preliminary phytochemical studies showed the presence of alkaloids, glycosides, and saponins in ACAS. The effect of ACAS was studied on alloxan-induced diabetic rats. The results indicate that treatment with ACAS produced a significant ($p < 0.01$) reduction in blood glucose levels. The anti-hyperglycemic activity was dose-dependent and reached its maximum within 4–6 hours after administration. The fall in blood glucose 6 h after administration was 27.8% and 38.8% at doses of 250 mg kg^{-1} and 500 mg kg^{-1}, respectively.

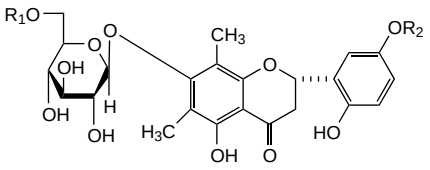
A significant reduction ($p < 0.01$) of blood glucose was registered also when continuous administration of ACAS was investigated. By day 15, blood-glucose was reduced by 48.9% and 54.4% at 250 mg kg^{-1} and 500 mg kg^{-1}, respectively. It should also be noted that, in contrast to the controls, no body weight loss was observed in the treated animals. Finally, no visible symptoms of toxicity were recorded after ACAS administration at a dose of 5 g kg^{-1}.

Because the seeds of *Celosia argentea* are hepatoprotective, improvement of liver functions and subsequent increase in glucose uptake and utilisation could be the mechanism of action of ACAS.

1 Hase, K. *et al.* (1997) Immunostimulating activity of Celosian, an antihepatotoxic polysaccharide isolated from *Celosia argentea*. *Planta Med.* 63, 216–219
2 Vetrichelvan, T. *et al.* (2002) Antidiabetic activity of alcoholic extract of *Celosia argentea* LINN. seeds in rats. *Biol. Pharm. Bull.* 25, 526–528

Aldose reductase inhibitors from *Myrcia multiflora* DC.

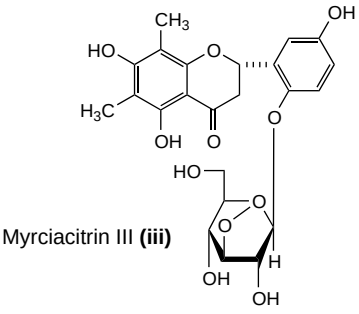
The methanolic extract and its ethyl-acetate soluble portion of the leaves of *Myrcia multiflora* DC. (*Myrtaceae*), a Brazilian natural medicine, were found to inhibit aldose reductase (AR) and α-glucosidase, as well as inhibiting the increase of serum-glucose in several animal diabetic models [3].



Myrciacitrin I **(i)** $R_1 = R_2 = H$
Myrciacitrin II **(ii)** $R_1 = H$, $R_2 = CH_3$
Myrciacitrin IV **(iv)** R_1 = *p*-coumaroyl, $R_2 = H$
Myrciacitrin V **(v)** R_1 = *p*-hydroxybenzoyl, $R_2 = H$

Yoshikawa and collaborators have previously reported on the isolation and structural elucidation of two flavanone glucosides, myrciacitrins I (**i**) and II (**ii**), together with several other components from the ethyl-acetate soluble portion of a methanolic extract of *Myrcia multiflora* DC. [4].

As a continuation of this study, the same group has now isolated from the



Myrciacitrin III **(iii)**

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ethyl-acetate soluble portion a new flavanone glucoside called myrciacitrin III (**iii**) and two new acylated flavanone glucosides called myrciacitrins IV (**iv**) and V (**v**) [5]. Their structures were attributed on the basis of chemical (mainly acidic and enzymatic hydrolysis) and spectroscopic (MS, IR, UV, NMR) data.

Their inhibitory activity was then tested on AR extracted from the lenses of Wistar rats. AR catalyzes the reduction of glucose to sorbitol in the polyol patway and is thought to be related to chronic diabetic complications such as peripheral neuropathy, retinopathy, and cataracts.

Myrciacitrins I–V were found to inhibit AR with IC_{50} values ranging from 1.6×10^{-5} M to 7.9×10^{-7} M, the most potent compound being Myrciacitrin II (ii). In the same assay, epalrestat, a commercial synthetic AR inhibitor, had an IC_{50} value of 7.2×10^{-8} M.

3 Matsuda, H. *et al.* (1999) Antidiabetic principles of natural medicines. IV. Aldose reductase and α-glucosidase inhibitors from the roots of *Salacia oblonga* Wall. (*Celastraceae*): structure of a new friedelane-type triterpene, kotalagenin 16-acetate. *Chem. Pharm. Bull.* 57, 1725–1729

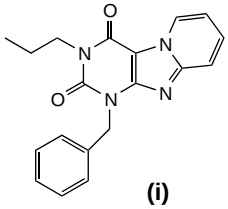
4 Yoshikawa, M. *et al.* (1998) Antidiabetic principles of natural medicines. II. Aldose reductase and α-glucosidase inhibitors from Brazilian natural medicine, the leaves of *Myrcia multiflora* DC. (*Myrtaceae*): structures of myrciacitrins I and II and myrciaphenones A and B. *Chem. Pharm. Bull.* 46, 113–119

5 Matsuda, H. *et al.* Antidiabetic principles of natural medicines. V. Aldose-reductase inhbitors from *Myrcia multiflora* DC. (2): Structures of myrcyacitrins III, IV, and V. *Chem. Pharm. Bull.* 50, 429–431

Novel human A_3 adenosine receptor antagonists

Adenosine exerts its physiological effects by activating specific cell membrane receptors. To date, four different adenosine receptor subtypes have been identified: A_1, A_{2A}, A_{2B} and A_3. The A_3 subtype has been investigated in recent years and antagonists for this receptor are potentially useful for the treatment of inflammation and the regulation of cell growth. The xanthine core structure has served as the basis for numerous selective antagonists for adenosine A_1, A_{2A} and A_{2B} receptors; however, xanthine-derived compounds are much less potent antagonists of the A_3 subtype.

A novel synthetic procedure has enabled the identification of a series of xanthine-fused structures – 1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-diones – which show moderate antagonist effects at A_1 receptors, low or negligible activity at A_{2A} receptors and significant affinity at the A_3 receptor [6]. Several compounds in this series show affinities in the low nanomolar range. In particular, the 1-benzyl-3-propyl-*1*H,*3*H-pyrido[2,1-*f*]purine-2,4-dione derivative (**i**), which can be considered a lead compound in this series, exhibited a K_i value of 4.0 ± 0.3 nM against the hA_3 receptor. Because xanthine derivatives have traditionally been considered poor A_3 antagonists, the described pyrido[2,1-*f*]purine-2,4-dione derivatives represent a new family of adenosine receptor antagonists that deserve further exploration.



(i)

6 Priego, E.M. *et al.* (2002). Pyrido[2,1-*f*]purine-2,4-dione derivatives as a novel class of highly potent human A_3 adenosine receptor antagonists. *J. Med. Chem.* 45, 3337–3344

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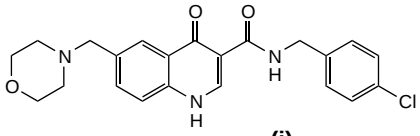
Novel antiviral molecules

A new antiviral compound active against herpes viruses

PNU183792 (**i**), a 4-oxo-dihydroquinoline, has been identified as an antiviral



(i)

agent with activity against members of the herpes virus family [1]. This includes human cytomegalovirus (hCMV), Varicella–Zoster virus (VZV) and herpes simplex viruses. A novel chemotype, PNU183792 is believed to act as a non-nucleoside viral polymerase inhibitor with an IC_{50} value of 0.4–0.7 μM.

Furthermore, in cell culture, compound **i** is able to inhibit hCMV ($IC_{50} = 0.3$ μM), VZV ($IC_{50} = 0.1$ μM), HSV-1 ($IC_{50} = 3.3$ μM) and HSV-2 ($IC_{50} = 4.6$ μM). In a mouse model of CMV infection, PNU183792 reduced mortality when dosed orally (25–100 mg kg^{-1}), before or at 48 h post-infection with virus.

1 Brideau, R.J. *et al.* (2002) Broad-spectrum antiviral activity of PNU-183792, a 4-oxo-dihydroquinoline, against human and animal herpesviruses. *Antiviral Res.* 54, 19–28

Azapeptide inhibitors of the hepatitis C virus serine protease

The hepatitis C virus (HCV) genome encodes a polyprotein that requires processing by cellular and virally expressed proteases for the virus to propagate. One such protease, the NS3 protein, is expressed by the virus and is a chymotrypsin-like serine protease that is responsible for processing a significant portion of the non-structural proteins (from NS3 to NS5B). As such, this protease is an attractive target for the development of potential antiviral agents.

A paper from Schering-Plough (http://www.schering-plough.com) identifies azapeptides as inhibitors of the protease [2]. Because it is known that the NS3-protease is susceptible to strong product-based inhibition, these peptides were designed around the known sequence of the protease NS5A–NS5B cleavage substrate. In addition, an aza-amino acid analogue, wherein the α-carbon atom of the amino acid is replaced by nitrogen,

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